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Key Words
Bullous pemphigoid · Ecthymata · Ecthyma gangrenosum

Abstract
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Introduction

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal, blistering skin disease occurring predominantly in elderly individuals in the fifth to seventh decades of life [1–4]. The incidence of BP appears to be equal in men and women. The onset of disease may be either subacute or acute, usually with widespread, tense blisters. Significant pruritus is frequently present. In some patients, the blisters arise following persistent urticarial lesions [5]. Involvement of the mucosal surface has been reported in 10–30% of BP patients. Nevertheless, one of the indicating clinical criteria for BP seems to be the lack of mucosal involvement [3, 6, 7].

BP is a result of a specific autoimmune antibody response directed towards the hemidesmosomal BP antigens BP230 and BP180 [8–12]. IgG autoantibodies bind to the skin basement membrane and activate complement. Activation of the complement system is thought to play a

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Table 1. Patient characteristics including age, sex, concomitant illnesses, medication and duration of disease on admission

Case	Age, years	Sex	Concomitant disease	Medication	Duration of disease, months
1	80	female	coronary artery disease, arterial hypertension, diabetes mellitus type 2, BMI 35.6, renal insufficiency, chronic depression	insulin, lisinopril, pantoprazole, citalopram, acetylsalicylic acid	7
2	86	female	coronary artery disease, arterial hypertension, multiple cerebral chronic ischemic lesions (with vertigo, chronic depression, parkinsonism)	clopidogrel, pravastatin, nitrazepam, pantoprazole, ramipril, carbidopa/levodopa	24
3	81	female	arterial hypertension, diabetes mellitus type 2, BMI 30.2, insomnia	amlodipine, diclofenac, zolpidem	1.5

critical role in attracting inflammatory cells to the basement membrane. These are postulated to release proteases, which degrade hemidesmosomal proteins and lead to blister formation.

Diagnosis is usually based on the clinical presentation, the histology and the results of direct (DIF) and indirect immunofluorescence (IIF) studies. Histologically, the blisters occur at the dermal-epidermal junction, and eosinophils are characteristically present in human patients' blisters. DIF demonstrates deposits of IgG in 70–90% and complement C3 deposition in 90–100% of patients in a linear pattern at the dermal-epidermal junction. This pattern is not specific for BP and may be seen in cicatricial pemphigoid and epidermolysis bullosa acquisita. BP can be differentiated from these conditions by incubating the patient's skin biopsy sample in 1 mol/l salt prior to performing the DIF technique for cleavage through the lamina lucida. DIF on salt-split skin reveals IgG on the blister roof in patients with BP. IIF studies document the presence of IgG circulating autoantibodies in the patient's serum that target components of the skin basement membrane. In our laboratory we use monkey and guinea pig esophagus as substrate. First, patient serum is applied to monkey and guinea pig esophagus sections. Then, a secondary fluorescence-labeled anti-immunoglobulin antibody is used, and the result is visualized. In selected cases, ELISA and Western blot analysis are additionally performed to detect autoantibodies against BP180 or BP230 [6, 13]. Antigenic epitopes and subdomains could recently be identified, and autoreactive T cell responses have been characterized [14–17]. Prognosis and disease activity correlate with serum levels of the autoantibodies to BP180 in patients with BP [9, 18].

There is a typical delay between onset of the disease and diagnosis of BP, which is partly due to a varied clinical presentation of BP. There are several distinct clinical presentations of BP, which have so far been described: generalized bullous form, vegetative form [19, 20], vesicular form [21], generalized erythrodermic form [22, 23], urticarial form, localized (usually pretibial) form [2, 24] and nodular form [25–28].

We report 3 patients with a distinct and hitherto unreported distinctive clinical presentation, characterized by ecthyma-gangrenosum-like lesions on the trunk (table 1). In most of our patients, BP was not the initial diagnosis taken into consideration. A high suspicion rate and repeated diagnostic procedures led to the definitive diagnosis of BP (table 2). All cases involved bacterial colonization, possibly favored by physical immobility. The aim of this case series is to establish a profile of patients with this peculiar clinical presentation of BP.

Case Presentation

Case 1

An 80-year-old female patient presented with multiple disseminated, sharply circumscribed, superficial to profound ulcers, measuring up to 15 cm in diameter, coated with yellowish to greenish, adherent fibrinous scabs (fig. 1), which had appeared 7 months ago. The lesions were most pronounced on the back and were exceedingly painful and itchy. There were no blisters. The clinical differential diagnosis covered ecthyma contagiosum, ecthyma gangrenosum, vasculitis, unspecific pyoderma and other autoimmune diseases. The wound swab culture showed repeatedly *Staphylococcus aureus*. There was no improvement with antibiotic therapy (first amoxicillin/clavulanic acid and cefepime, then adjusted to flucloxacillin following an antibiogram). Histology showed an intraepithelial pustule with a mainly eosinophilic

Table 2. Diagnostic findings including histology, DIF, IIF and additional diagnostic procedures such as Western blot analysis

Case	Histology	DIF	IIF	Other
1	superficial ulceration with bacterial masses, dermal mainly eosinophilic infiltrate	IgG deposits in a linear pattern at the epidermal basement membrane, C3 deposits at the dermoepidermal junctional zone	circulating autoantibodies (IgG) against components of the basal membrane	peripheral blood eosinophilia
2	eosinophilic spongiosis, as seen in the prebullous phase of BP	negative	circulating autoantibodies (IgG) against components of the basal membrane	Western blot: band at 230 kDa; ELISA positive for recombinant BP230
3	superficial ulceration of the epidermis with bacterial masses, inflammatory cell infiltrate, containing eosinophils	linear IgG and C3 deposits at the epidermal basement membrane	negative	Western blot negative for bands at 230 and 180 kDa

and discrete neutrophilic infiltrate and a perivascular infiltrate with lymphocytes and eosinophils (fig. 2). The complete blood count revealed an eosinophilia of maximally $1.8 \times 10^3/\mu l$ (normal range $0.00–0.70 \times 10^3/\mu l$). On DIF, linear deposits of IgG and C3 along the basal membrane were found. The IIF showed circulating IgG autoantibodies directed at antigens within the basement membrane zone. These findings led to the diagnosis of a BP with ecthyma-gangrenosum-like clinical appearance. Differential diagnoses of other autoimmune bullous diseases, in particular epidermolysis bullosa acquisita, were ruled out by lack of mucosal affection and lack of typical distribution along mechanically exposed sites. Following this diagnosis, we switched therapy from antibiotics to intravenous corticosteroids for 9 days followed by a combination therapy of nicotinamide 500 mg 3 times a day and doxycycline 100 mg twice a day. Topically we used steroids under adhesive dressings. As a result of this therapy, the ulcers were almost completely healed after 8 weeks, and the patient could be discharged. The therapy was continued until death, which occurred unfortunately soon after.

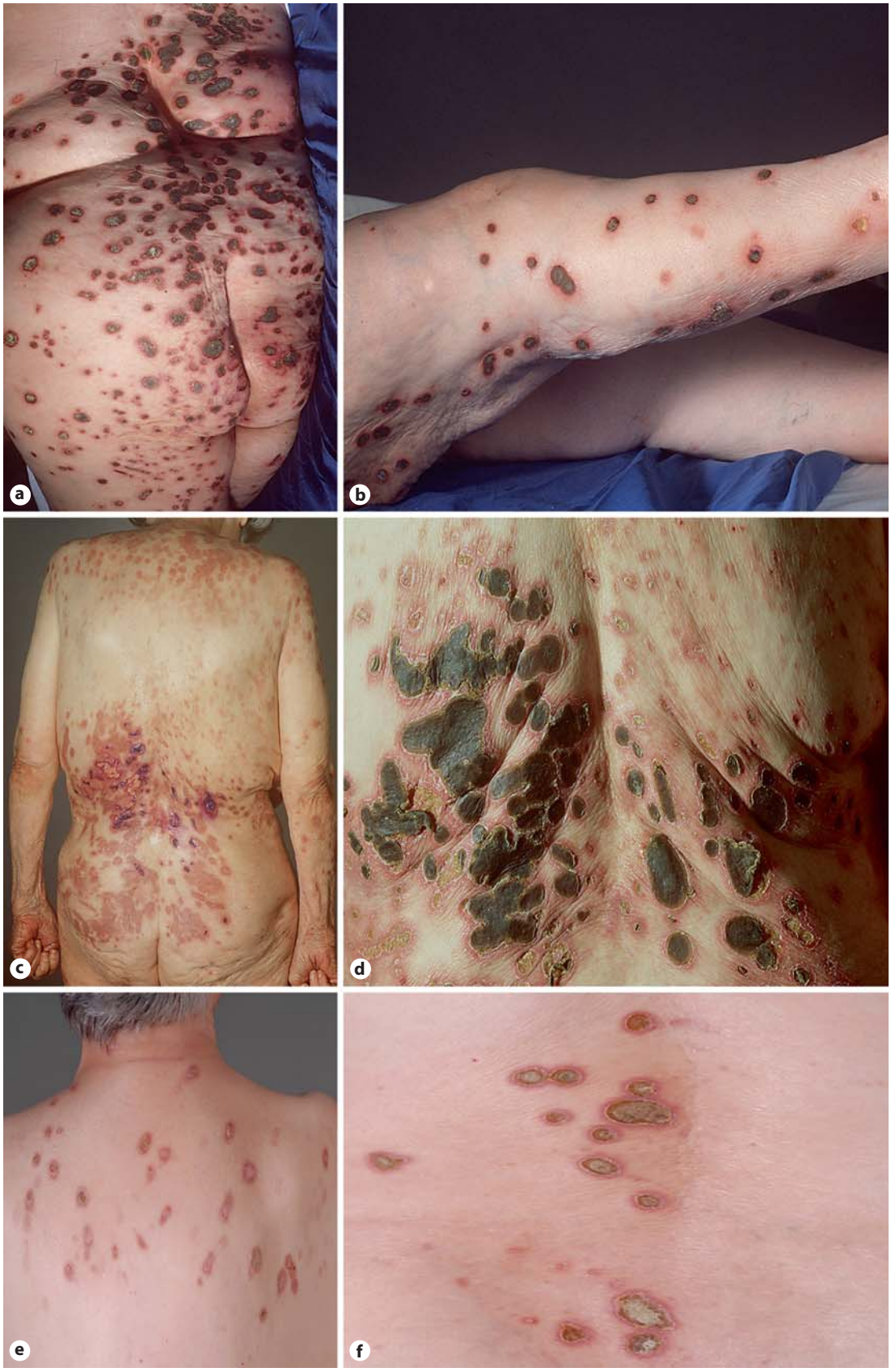
Case 2

The 86-year-old female patient had a 2-year history of a very itchy rash with very itchy, red papules on the arms and shoulders initially. These efflorescences multiplied and spread to the whole back and legs over the next months. There was no improvement achieved by topical and shortly administered systemic steroids. On admission to our hospital we observed multiple, disseminated, partly confluent, sharply circumscribed ulcers on the back, arms and legs. They ranged in size from 1 to 4 cm and were coated with thick brownish-black scabs. Neither blisters nor urticarial eruptions were visible at admission. Our differential diagnoses were vasculitis, blistering autoimmune disease or ecthyma. Histology showed subepidermal blistering, spongiosis and mixed infiltrate. DIF was negative. However, IIF revealed circulating IgG autoantibodies binding to the dermoepidermal junction on monkey and guinea pig esophagus sections in a linear pattern. Additionally, a serum Western blot was positive for antibodies against the 230-kDa antigen. These results led to the diagnosis of BP with ecthyma-gangrenosum-like clinical appearance. Under systemic treatment with nicotinamide and vibramycin, and topical steroids, the ulcers healed over the next 2 weeks almost completely up to discharge. To our knowledge, there has not been a relapse, even though our follow-up stopped 1 year after diagnosis.

Case 3

This 81-year-old female patient was admitted for further diagnostic tests and therapy because of itching skin lesions of 6 weeks' duration. Initially there were blackish spots disseminated on the back and less so on the abdomen. On admission we found multiple erosions with a fibrinous coat and red surrounding skin mainly on the upper back but also disseminated over the lower back, buttocks, legs and abdomen. There were no blisters. The histology revealed an unspecific inflammatory reaction. The DIF was however specific for BP with IgG and C3 deposits in a linear fashion along the basal membrane. Epidermolysis bullosa acquisita as a differential diagnosis could be ruled out clinically because of no involvement of the mucosae and lack of typical distribution along mechanically exposed sites. Therapy with systemic corticosteroids and mycophenolate was initiated in combination with ciprofloxacin to treat the Gram-negative bacterium *Serratia marcescens,* which grew from a swab. Under this therapy, the skin healed over the next 3 weeks without new efflorescences at discharge and with no relapse until today.

Fig. 1. Clinical presentation of ecthyma-gangrenosum-like BP. Overview and close-up of patients 1 (**a**, **b**), 2 (**c**, **d**) and 3 (**e**, **f**) are shown. All patients present a similar picture with multiple disseminated, sharply circumscribed, superficial to profound ulcers, measuring up to 1.5 cm in diameter, coated with yellowish to greenish, adherent fibrinous scabs, mainly located on the back.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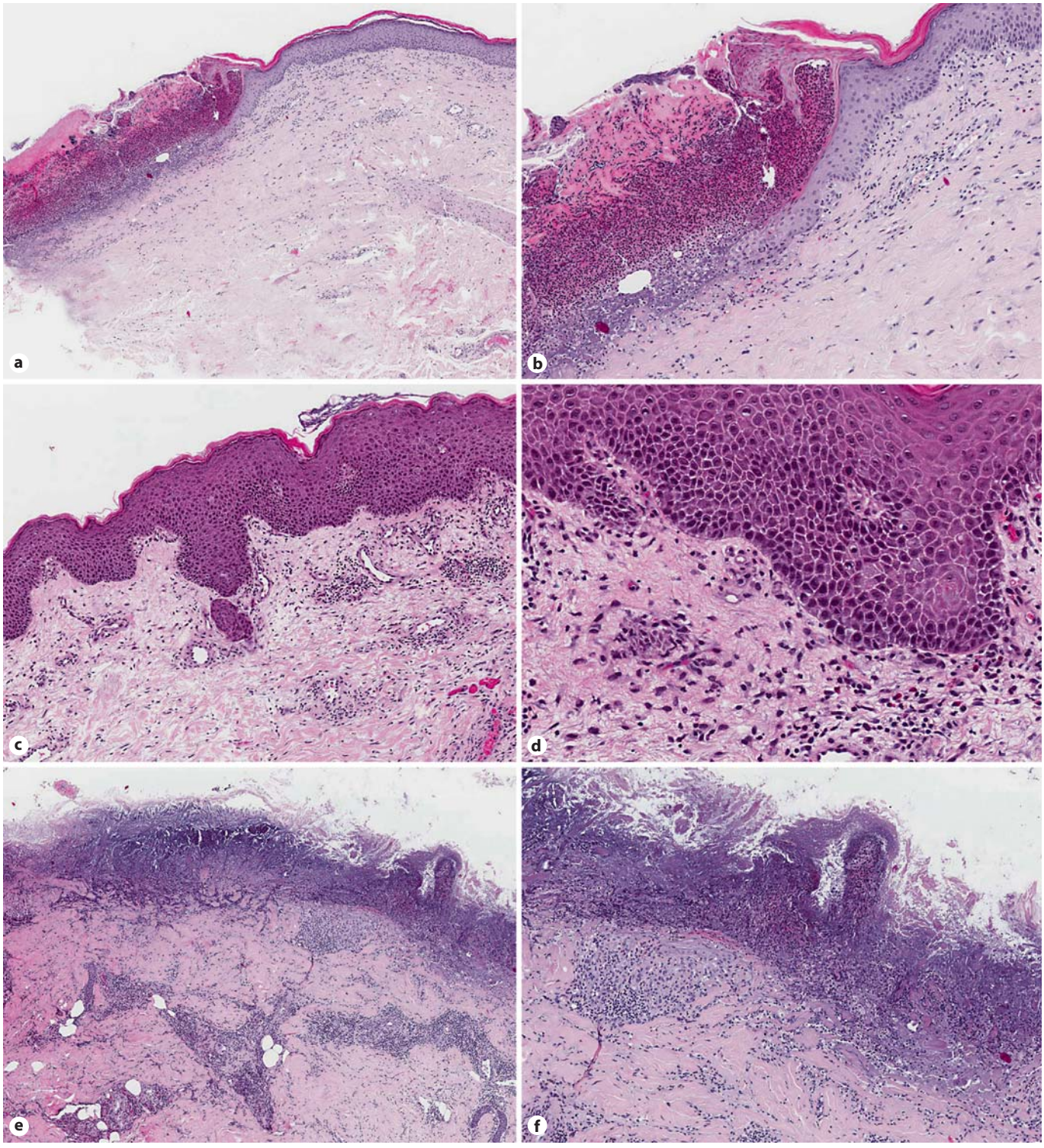

Fig. 2. Histological presentation of ecthyma-gangrenosum-like BP in patients 1 (**a**, **b**), 2 (**c**, **d**) and 3 (**e**, **f**). HE stains at low- and high-power magnification show partly unspecific changes and partly pathognomonic changes for BP such as subepidermal blister formation and eosinophilic spongiosis. The histological observations are listed in detail in table 2.

Table 3. The factors of immobility contributing to delayed wound healing: rheumatic disease, obesity, sedatives, psychiatric disease and neurological disease

Case	Rheumatic disease	BMI	Sedatives or medication with sedative side effect	Psychiatric disorder	Neurological disorder
1	none	36	citalopram	chronic depression	diabetic neuropathy
2	none	24	nitrazepam	chronic depression	vertigo, secondary parkinsonism
3	chronic posttraumatic pain of left shoulder and right hip	30	zolpidem	insomnia	none

Obesity was categorized by body mass index (BMI; weight/square height, kg/m^2): BMI ≤ 18.5 signifies underweight, BMI 18.5–24.9 normal weight, BMI 25.0–29.9 overweight, BMI 30.0–39.9 obesity and BMI ≥ 40 extreme obesity.

Discussion

We present 3 cases of BP with a clinically distinct presentation. The clinical picture of all patients was very much alike, with ecthyma-gangrenosum-like lesions on the trunk of elderly bedridden female patients. In all cases, BP was not considered as first differential diagnosis, but rather ecthyma gangrenosum, necrotizing vasculitis, disseminated pyoderma gangrenosum and cutaneous T cell lymphoma were considered. Autoimmune bullous disease was only considered in the differential diagnosis with a low priority, while eventually proving to be the final diagnosis.

Bacterial colonization seemed important: penetration of *Pseudomonas aeruginosa* is facilitated by several extracellular products such as exoenzyme S, elastase, exotoxin A, alkaline protease, hemolysins and leucocidin. The enzymes elastase and exoenzyme S are important virulence factors by disrupting the epithelial barrier function. From studies of venous leg ulcers, it is well known that the presence of *P. aeruginosa* can induce ulcer enlargement and/or cause delayed healing [29, 30]. By a variety of exotoxins (e.g. hemolysins, proteases, leucocidins), *S. aureus* also leads to epithelial damage. The pathogenicity of *S. aureus* is increased in the presence of anaerobic bacteria such as *P. aeruginosa* [29, 30]. We hypothesize that the initial epidermal barrier disruption by the developing lesions of BP or scratching due to pruritus related to BP (fig. 1e, f) combined with physical immobility predisposed the skin of the back in our patients to extensive bacterial overgrowth with *P. aeruginosa* and/or *S. aureus*, leading to delayed healing, enlarging wounds and diagnostic problems [31, 32].

All patients were elderly women with impaired physical mobility (table 3). It is conceivable that relevant physical immobility leads to occlusion favoring bacterial overgrowth of either primary bullous lesions of BP or secondary excoriations due to pruritus associated with BP. Only extended diagnostic workup with additional and repeat diagnostic tests led to the final diagnosis of BP. This hitherto undescribed clinical presentation for BP and the initially negative tests for BP in a majority of patients led to delayed diagnosis and delayed start of an effective treatment (table 2) [8, 11, 14].

We propose that ecthyma-gangrenosum-like BP is yet one more distinct clinical presentation of BP observed on the trunk of elderly, bedridden female patients, and that it is associated with bacterial overgrowth, primarily with *P. aeruginosa* and *S. aureus*. Recognizing this form of BP is important, since a high suspicion rate, extended and repeated diagnostic procedures are prerequisites for establishing the diagnosis of BP. Once the diagnosis is made, appropriate therapy of secondary infection and of BP along the proposed guidelines [33] will usually be successful.

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